

41b – Selected Syndromes in Stem Cell Transplant Recipients

Speaker: Kieren Marr, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Selected Syndromes in Stem Cell Transplant Recipients

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Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant – Amplyx, Cidara, Merck and Company, Sfunga Therapeutics
- Ownership Interests – MycoMed Technologies

PEARLS

- Fundamentals - risks
 - Early – mucositis, neutropenia
 - Late – GVHD (steroids, asplenia, T cell dysfunction)
- Syndromes
 - Early pulmonary syndromes
 - Bacterial, fungal pneumonia
 - Non-infectious: Alveolar hemorrhage, IPS
 - Late pulmonary syndromes
 - CMV, respiratory viruses, IFI
 - Non-infectious: BOOP
- Hemorrhagic cystitis
 - BK
 - Non-infectious: conditioning
- Diarrhea – colitis – hepatitis
 - Herpes viruses
 - Non-infectious: GVHD
- Neurologic syndromes
 - Herpes viruses (+HHV-6), west nile, angio-invasive, toxoplasmosis, PML (JCv)
 - Non-infectious: PRES, antibiotics

Fundamentals of BMT

Stem cells
↓
Conditioning → engraftment → +/- GVHD

- Immune risks for infection are temporal
 - Neutropenia (early)
 - Bacterial infections
 - Fungal infections
 - Impaired cellular and humoral immunity (late)
 - Bacterial infections
 - Fungal infections
 - Viral infections

Fundamentals of BMT

- Autologous (self) vs. allogeneic (other)
- Types of allogeneic donors
 - Related, HLA – matched (MR)
 - Related, HLA - mismatched (haploidentical)
 - Unrelated, HLA – matched (MUD) or Unrelated, HLA – mismatched (MM-URD)
- Types of stem cells
 - Bone marrow
 - Peripheral blood
 - Cord blood
- Types of conditioning regimens
 - Myeloablative
 - Nonmyeloablative

Approach for the boards

- Know common infections and non-infectious mimics
- Approach stems in context
 - Patient’s age, disease, history impact risks after BMT
 - What kind of BMT did the patient have?
 - Is the patient early vs. late after BMT?

Type of BMT and timeline impacts immunity, drugs and exposures

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Case #1

42 year old M AML 20 days after a matched unrelated donor BMT (nonmyeloablative) develops fever, cough, pulmonary infiltrates.
Pre-transplant: HSV+, VZV+, CMV D+/R-
Exam– 98% sat on 2L nc, T 38.3, crackles RLL
Labs- Cr 2.2, WBC 1200 cells/mL, plt 122
He's currently receiving acyclovir and fluconazole for prophylaxis.



Case #1

What is the most likely cause of his current process?

- A. *Candida albicans*
- B. *Klebsiella pneumoniae*
- C. CMV
- D. Parainfluenza virus
- E. Hemorrhage

Pulmonary Complications

- Bacterial pathogens
 - *P. aeruginosa*, *Streptococci*, *Legionella*, *S. aureus*
 - Aspiration events with severe mucositis early after BMT
 - Encapsulated sinopulmonary pathogens late after BMT
- Filamentous fungi early and late (*A. fumigatus*)



Pulmonary Complications (Con't)

- Respiratory virus infection follows seasonal epidemiology
 - Increased risk for lower tract involvement
 - Influenza, RSV, Parainfluenza 3, Human metapneumovirus
 - Adenovirus: reactivation and acute infection (particular issue with kids)
- Herpes viruses
 - CMV with prolonged impairment in cellular immunity
 - HSV classically described with prior airway manipulation

Early non-infectious lung injury

- Diffuse alveolar hemorrhage
 - Bleeding in alveolar space, heterogeneous etiology
 - Vasculitis, drug-induced injury, cancer-chemotherapy / thrombocytopenia
- Idiopathic pneumonia syndrome
 - Within 1st 120 days of HSCT, non-infectious
 - Risks: conventional ablative conditioning, acute GVHD (inflammatory pathogenesis?)

Case #2



PREVIEW QUESTION

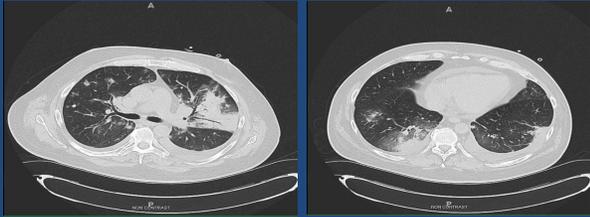
A 46 year old male 18 months s/p HLA mismatched BMT. History of GVHD skin, GI tract, and BOOP 3 months ago, treated with steroids. One month s/p Parainfluenza 3 URI, with chest CT - tree-in-bud opacities in LLL. Received levofloxacin for 10 days.

He now has increasing shortness of breath and cough.

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Case # 2 (con't.) INFECTIOUS DISEASE BOARD REVIEW PREVIEW QUESTION



Case # 2 (con't.) INFECTIOUS DISEASE BOARD REVIEW PREVIEW QUESTION

Blood cultures no growth. Sputum – LF GNR. Serum galactomannan is negative. What is the most likely cause of his current process?

- A. *Cryptococcus neoformans*
- B. *E. coli*
- C. MRSA
- D. *Aspergillus fumigatus*
- E. *Fusarium* spp.

DDx of Late pulmonary syndromes

- Infectious
 - CMV disease
 - Respiratory virus infections
 - PJP
- Non-infectious
 - Bronchiolitis obliterans syndromes

CMV Infection after BMT

- Reactivation occurs in seropositive patients (R+).
 - Reactivation alone triggers cytokine storm, GVHD, disease
 - Risk for *disease* dependent on immunity
 - Highest risk group for disease after BMT: D- / R+
 - No transferred immunity to CMV
 - This is different than SOT, where highest risk group is D+ / R-
- Primary infection in seronegative patients (R-) from community, positive graft (D+) or blood products (rare)

CMV Disease

- Pneumonitis
 - Indolent cough, fever, SOB, interstitial infiltrates
- Gastrointestinal disease
 - Esophagitis, colitis, hepatitis (rare)
- Encephalitis, retinitis less frequent

CMV Disease after BMT (con't.)

- Treatment concepts
 - Pre-emption with ganciclovir driven by PCR
 - Not prophylaxis (SOT) with ganciclovir (toxicities)
 - Prophylaxis of R+ patients with letermovir
 - Induction therapy with maintenance GCV
 - Resistance to GCV is *rare* (as opposed to SOT)
 - Most failures are due to steroids, T cell depletion
 - Recipe for GCV – resistance: long exposure to suboptimal doses of GCV in a patient with poor cellular immunity

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Pneumocystis Pneumonia

- Common late after BMT
 - Steroid receipt, T-cell depletion
- Prophylaxis at least 6 months
 - Bactrim
 - Toxicities
 - Dapsone, atovaquone, aerosolized pentamidine
 - Less effective, other infections occur**
- Late diagnoses occur
 - BAL DFA less sensitive

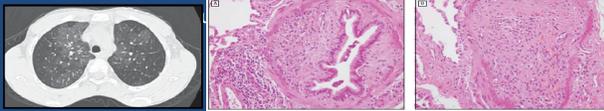
Toxoplasmosis

- Clusters of disease reported in BMT patients
 - T-depleted BMT
 - Some early. Acquisition vs. reactivation?
- Regions with high seroprevalence screen for disease with pre-emptive therapy
- Pneumonia, encephalitis, fever

Issa et al, ID Week 2014
Meers et al. Clin Infect Dis, 2010 Apr 15;50(8):1127-34

Bronchiolitis Obliterans

- Chronic GVHD of lung
 - Allorecognition of lung antigens
- Circumferential fibrosis of terminal airways ultimately leading to airflow obstruction



Williams JAMA 2009

A. Obliteration of bronchiolar lumen
B. Inflammation between the epithelium and the smooth muscle

Case #3

35 yr old F, 80 days after allogeneic BMT with 5 days of anorexia, nausea, epigastric pain, and diarrhea. CMV D-/R+, HSV+, VZV+.

Exam: faint maculopapular rash on upper body. Afebrile.

Meds: acyclovir, TMP-SMX and fluconazole.

ANC 1000, ALC 250. LFTs normal.

What is the most appropriate initial work-up and management?

- A. Perform serum VZV PCR
- B. Empiric corticosteroid treatment
- C. Send C. diff toxin and start oral vancomycin
- D. CMV PCR, stool C. diff, bacterial culture
- E. #D and upper, lower endoscopy

Graft vs. Host Disease (GVHD)

- Acute (early after HSCT)
 - Fever
 - Rash
 - GI: hepatic, colon
- Chronic (later after HSCT)
 - Skin changes (lichen planus, scleroderma)
 - Hepatic (cholestatic)
 - Ocular (keratoconjunctivitis)
 - GI (oral, dysphagia)
 - Pulmonary syndromes

DDx of GI Disease in BMT

HEPATITIS

- GVHD
- Herpes viruses (CMV, VZV)
- Hepatitis B virus
 - Increased viral replication and liver damage
 - Hepatitis not common during neutropenia

DIARRHEA

- GVHD
- CMV
- C. difficile
- Norovirus (chronic diarrhea mimicking GVHD)
- Adenovirus

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Adenovirus Infection after BMT

- More common in children, high risk BMT
 - Severe GVHD and steroids
- Enteritis, cystitis, upper respiratory infection, pneumonia, encephalitis, hepatitis
- No controlled treatment studies
 - Taper immunosuppression
 - Cidofovir most active in vitro
 - Ribavirin not effective in larger studies

Case #4

53 year old F 7 yrs s/P allo BMT presents with fever, chills, rigors. H/O severe chronic GVHD skin. PE – T 39.2. tachycardia, tachypnea, hypotension. Skin thick, cracked (Sjogren-like). Social- dog and two cats, no recent exposures. Labs- WBC 8200 / mm3, platelet 43,000/mm3. CT of her chest, abdomen, pelvis - splenic atrophy. Blood cultures positive for gram-negative rods after 5 days.

Most likely cause of her current condition:

- A. *Fusobacterium nucleatum*
- B. *Eikenella corrodens*
- C. *Capnocytophaga canimorsus*
- D. *Acinetobacter baumannii*

Case #5

40 year old M day 60 after allogeneic BMT from unrelated donor, with bloody urine for 6 days. Has skin GVHD, receiving a prednisone taper (1 mg/kg/day). Exam, faint diffuse erythematous rash. Cr 1. LFTs normal. CMV pcr negative.

The most likely etiology is:

- A. Cyclophosphamide
- B. CMV
- C. EBV
- D. BK
- E. JC virus

DDx of Hemorrhagic Cystitis

- Conditioning related (early)
 - Cyclophosphamide
- BK virus (later)
- Adenovirus (later)

DDx of Neurologic Syndromes

- Infection
 - Herpes viruses: HSV, CMV, HHV6*
 - West Nile virus
 - JCV – PML (especially with T-depleting Abs)
 - Pulmonary – CNS lesions
 - Invasive fungal infections
 - Nocardia
 - Toxoplasmosis
- Drugs: carbapenems, cefepime, PRES*

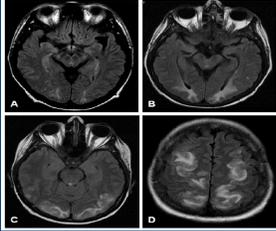
HHV-6 after BMT

- HHV-6 seroprevalence > 95% after age 2
 - Early reactivation common after BMT 38-60% SCT (type B)
 - Clinical correlates reported: rash, marrow suppression, delayed platelet engraftment, idiopathic pneumonitis
- Meningoencephalitis**
 - Nonspecific presentation (confusion, memory loss, EEG / MRI: temporal)
 - Early - within 60 days of BMT
 - RFs: MM/URD or UCB SCT, anti-T-cell
- Diagnosis: PCR of CSF
- Chromosomal integration
- ACV-resistant. Treat with ganciclovir, foscarnet, cidofovir

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Posterior reversible encephalopathy (PRES)



- Usually early after HSCT (within 1st 3 months)
- Calcineurin inhibitors: Cyclosporin*, tacrolimus
- Seizures, visual changes, MS changes

VZV Infection after BMT

- Multidermatomal lesions
- Primary viral pneumonia
- Encephalitis
- Hepatitis
 - Classic: abd pain, transaminitis late
 - Can occur without skin lesions
- VZV seropositive
- Severe GVHD, acyclovir prophylaxis effective long term
- Recent study: 1% rate of infection, high rate after 1 yr

Baumrin et al. Biol Blood and Marrow Trans 2019 (in press)

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Thank you

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